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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MARK F. PITTENGER, ALASTAIR M. MACKAY, J. MARY MURPHY, and FRANCIS P. BARRY

Appeal 2007-2709
Application 09/319,521
Technology Center 1600

Decided: January 3, 2008

Before TONI R. SCHEINER, ERIC GRIMES, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for producing chondrocytes from mesenchymal stem cells. The Examiner has rejected the claims as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

The Specification teaches that "[d]amage to the articular surfaces of synovial joints can arise from trauma, from diseases such as osteoarthritis, and as a result of the aging process" and that "effective therapies that could

restore joint function would be welcome" (Specification 3). The Specification states that "[a]rticular cartilage is created and maintained during prenatal and postnatal growth by mesenchymal cells that have differentiated into articular chondrocytes" and that there has been "a great deal of interest in the hypothesis that damaged joint surfaces may be repaired by implanting autologous cells that will reconstitute a suitable extracellular matrix" (*id.*).

The Specification teaches that "human mesenchymal stem cells (hMSCs) . . . maintain viability and can be induced to significantly improved commitment and differentiation [into chondrocytes] when contacted *in vitro* with certain chondroinductive media compositions having elevated levels of simple sugars or other factors which contribute to the production of ATP by the citric acid cycle" (*id.* at 4).

DISCUSSION

1. CLAIMS

Claims 60-99 are pending and on appeal. Claims 60 and 80 are representative and read as follows:

Claim 60. A process for producing chondrocytes from mesenchymal stem cells by culturing mesenchymal stem cells in a chemically defined serum-free medium in vitro

wherein the mesenchymal stem cells are associated in a three-dimensional format, and

wherein said chemically defined serum-free medium comprises (1) a chemically defined minimum essential medium; (2) ascorbate or an analog thereof; (3) an iron source; (4) insulin or an insulin-like growth factor; (5) at least one chondroinductive agent or factor; and (6) a simple sugar, said simple sugar being present in said medium in an amount of from about 3g/l to about 7g/l.

Claim 80. A process for producing chondrocytes from mesenchymal stem cells by culturing mesenchymal stem cells in a chemically defined serum-free medium *in vitro*

wherein the mesenchymal stem cells are associated in a three-dimensional format, and

wherein said chemically defined serum-free medium comprises (1) a chemically defined minimum essential medium; (2) ascorbate or an analog thereof; (3) an iron source; (4) insulin or an insulin-like growth factor; (5) at least one chondroinductive agent or factor, wherein said at least one chondroinductive agent or factor comprises TGF-β3; and (6) a simple sugar, said simple sugar being present in an amount of from about 3g/l to about 7g/l.

2. ANTICIPATION

Claims 60-79 stand rejected under 35 U.S.C. § 102(e) as anticipated by Johnstone,[1] as evidenced by Cellgro,[2] US Biological,[3] and Williams.[4] Claims 61-79 have not been argued separately and therefore stand or fall with claim 60. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner finds that Johnstone discloses "a process for producing chondrocytes from mesenchymal stem cells . . . comprising culturing human mesenchymal stem cells in vitro in a three dimensional format with at least one chondroinductive agent" (Answer 4). The Examiner also finds that Johnstone discloses "that any serum-free animal medium can be used, including DMEM, IMEM, Mc Coy5A and BGJ_b medium" (*id.*). The Examiner further finds that, as evidenced by Cellgro, US Biological and Williams, "the glucose content in DMEM, IMEM, Mc Coy5A is about 4.5 g/1. . . . Moreover, as is evidenced by Williams et al., one skilled in the art

[1] Johnstone et al., US 5,908,784, June 1, 1999
[2] Cellgro catalog, 2001
[3] US Biological catalog, 2004
[4] Williams et al., 2003, *Tissue Engineering* 9(4):679-688

at the time the invention was made would know that a chondrogenic medium inherently consists of high-glucose Dulbecco's modified Eagle's medium (DMEM)" (*id.* at 4-5).

We agree with the Examiner that Johnstone discloses all of the limitations of claim 60. The method defined by claim 60 requires culturing mesenchymal stem cells, in a three-dimensional format, in a serum-free medium comprising (1) a chemically defined minimum essential medium, (2) ascorbate or an analog thereof, (3) an iron source, (4) insulin or an insulin-like growth factor, (5) a chondroinductive agent, and (6) a simple sugar in an amount of about 3-7 g/l.

Johnstone discloses "a process for inducing chondrogenesis in mesenchymal stem cells by contacting mesenchymal stem cells with a chondroinductive agent in vitro where the stem cells are associated in a three dimensional format" (Johnstone, col. 2., ll. 33-37). Johnstone also discloses that

> the contacting preferably comprises culturing a pellet of human mesenchymal precursor cells in a chemically defined serum-free medium which comprises (1) a chemically defined minimum essential medium; (2) ascorbate or an analog thereof; (3) an iron source; (4) insulin or an insulin-like growth factor; and (5) at least one chondroinductive agent or factor

(*Id.* at col. 2, ll. 43-49.) Thus, the only element of the instantly claimed method that is not expressly disclosed by Johnstone is the amount of simple sugar in the medium.

Johnstone also discloses that "the term 'minimum essential medium' refers to any serum-free animal cell culture preparation or medium of known composition which will support the viability of human mesenchymal stem

cells in vitro. Examples are any of the Eagle's based media, i.e., Dulbecco's Modified Eagle's Medium (DMEM); [etc.]" (*id.* at col. 4, ll. 27-34).

Appellants do not dispute that Johnstone discloses a process meeting all of the limitations of claim 60 except for the amount of simple sugar. Appellants argue, however, that Johnstone does not disclose a sugar amount in the claimed range (Appeal Br. 5). Appellants also argue that the references cited for evidence that the glucose content of DMEM is about 4.5 g/l, i.e. Cellgro, US Biological, and Williams, were published after the filing date for the instant application and that the Examiner's reliance on these references to show the level of ordinary skill in the art is misplaced (*id.* at 4). Appellants further argue that US Biological and Cellgro provide no information as to the level of ordinary skill in the art with respect to producing chondrocytes and that Williams does not suggest to one of ordinary skill in the art that a culture medium having a simple sugar concentration of 3-7 g/l may be used as part of a culture medium for mesenchymal stem cell differentiation into chondrocytes (*id.*).

We are not persuaded by these arguments. Cellgro discloses that Dulbecco's Modification of Eagle's Medium (DMEM) typically contains 4.5 g/l of glucose (7 out of 8 types) while one out of eight types contains 1.0 g/l of glucose. In addition, Johnstone refers to "Dulbecco's Modified Eagle's Medium-Low Glucose (DMEM-LG)" (Johnstone, col. 6, ll. 38-44) as a medium to use for culture expansion of mesenchymal stem cells (*id.* at col. 5, ll. 35-36). In light of the evidence of record, Johnston's reference to "low glucose" or "DMEM-LG" medium would be reasonably understood by those skilled in the art to refer to DMEM containing only 1 g/l of glucose,

supporting the conclusion that Johnstone's reference (at col. 4, ll. 27-34) to "DMEM" refers to the more common, 4.5 g/l glucose formulation.

Given that Cellgro shows that DMEM having 4.5 g/l is the most common type, the recitation in Johnstone of DMEM, without qualification as to glucose concentration, would be understood by one of skill in the art to refer to DMEM having 4.5 g/l glucose because the evidence shows that that type is most typically used in the art. Cellgro is relied upon as evidence of the state of the art on the filing date of the application. Appellants have not provided evidence that DMEM would be interpreted any differently before or after the filing date of the application.

Because we agree with the Examiner that Cellgro provides evidence that one of skill in the art would interpret the term DMEM in Johnstone as being DMEM having 4.5 g/l of glucose, Johnstone expressly or inherently discloses all the limitations of claim 60, and thus, claim 60 is anticipated by Johnstone.

3. OBVIOUSNESS

Claims 80-99 stand rejected under 35 U.S.C. § 103 as obvious over Johnstone and Hunziker[5], as evidenced by Cellgro, US Biological, and Williams. Claims 81-99 have not been argued separately and therefore stand or fall with claim 80. 37 C.F.R. § 41.37(c)(1)(vii). Claim 80 is directed to the same method as claim 60 but specifies that the "chondroinductive agent or factor comprises TGF-β3."

The Examiner relies on Johnstone, in combination with the evidence provided in Cellgro, US Biological, and Williams, for the disclosure set forth above. The Examiner also relies on Johnstone for disclosing that a

[5] Hunziker, US 5,368,858, Nov. 29, 1994

chondroinductive agent is "a member of the transforming growth factor beta super family (TGF-β) such as BMP-2 or BMP-4, [or] TGF-β1," and that "[p]articularly preferred is the combination of dexamethasone and TGF-beta-1" (Answer 4).

The Examiner finds that Johnstone "does not explicitly teach the use of TGF-β3" (*id.* at 5). The Examiner relies on Hunziker for disclosing "the use of TGF-β3 in a method of proliferating chondrocytes" and disclosing that "mesenchymal cells when exposed to TGF-β3 will be transformed into . . . chondrocytes" (*id.*). The Examiner further relies on Hunziker for disclosing that the activity among members of the TGF-β family is similar (*id.*).

The Examiner concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Hunziker to the teaching of Johnstone "to obtain a claimed process for producing chondrocytes from mesenchymal stem cells using TGF-β3" as one of the chondroinductive agents (*id.* at 6). The Examiner reasons that one of ordinary skill in the art would have been motivated to use TGF-β3 in Johnstone's method because Hunziker teaches that "the activity among members of the TGF-β family are similar," because "TGF-β3 can be used in a method of proliferating chondrocytes, and that mesenchymal cells when exposed to TGF-β3 will be transformed into a chondrocytes" (*id.*).

We conclude that the Examiner has set forth a prima facie case that claim 80 would have been obvious to the ordinary artisan. Johnstone's disclosure is discussed above. Johnstone also discloses that one preferred chondroinductive agent is "a member of the transforming growth factor-β

superfamily such as a bone morphogenic protein (preferably BMP-2 or BMP-4), TGF-β1, inhibin A or chondrogenic stimulating activity factor. . . . Particularly preferred is the combination of dexamethasone and TGF-β1" (*id.* at col. 2, ll. 18-27).

Hunziker discloses a composition comprising a "transforming factor . . . to transform repair cells . . . into cartilage-producing chondrocytes" (Hunziker, abstract). Hunziker also discloses that "[r]epair cells include mesenchymal cells . . ." (*id.* at col. 5, ll. 31-32) and that "transforming factors useful in the compositions and methods of this invention include . . . TGF-βs" (*id.* at col. 8, ll. 45-47). Hunziker specifically suggests using TGF-β3 ("TGF-βIII") as the transforming factor (*id.* at col. 9, ll. 6-12).

We agree with the Examiner that it would have been prima facie obvious to one of skill in the art at the time the invention was made to combine the teachings of Johnstone and Hunziker and thereby arrive at the invention defined by claim 80. As set forth above, Johnstone discloses all of the elements of claim 80 in the claimed process for producing chondrocytes except TGF-β3 as the chondroinductive agent. Johnstone particularly teaches that the chondroinductive agent may be a member of the TGF-β superfamily. Hunziker teaches that TGF-β3 may be used to induce transformation of repair cells, including mesenchymal cells, into chondrocytes. Thus, one of skill in the art would have been motivated to use TGF-β3 chondrocyte-inducing agent of Hunziker in the process of Johnstone because Hunziker specifically suggests that TGF-β3 may be used as a transforming agent.

Appellants do not dispute that Hunziker would have suggested the use of TGF-β3 for the production of chondrocytes, but argue that the combination of the references does not cure the defect of Johnstone in failing to disclose the claim limitation of a simple sugar being present in the medium in an amount of from 3g/l to 7g/l (Appeal Br. 8).

For the reasons discussed above, we are not persuaded by this argument. The rejection under 35 U.S.C. § 103 is affirmed.

SUMMARY

The Examiner's rejections are supported by the preponderance of the evidence of record. We therefore affirm the rejection of claims 60-79 under 35 U.S.C. § 102(e) and the rejection of claims 80-99 under 35 U.S.C. § 103.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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